Remarks

Claims 1-18 and 25-29 are pending. Claims 1, 4, and 6 have been amended as discussed below. Claims 9-13 and 27 have been withdrawn from consideration as being drawn to a non-elected invention. Claims 1 has been amended to recite that the disease is characterized by expression of an abnormal antigen or abnormally elevated amount of an antigen rather than a molecule. Claim 4 has been amended to recite that the antigen is a polypeptide. Support for amendments to claims 1 and 4 can be found, for example, on page 7, lines 24-28 in view of lines 3-22. The applicant has amended claim 6 to recite that the polypeptide is present at an abnormally elevated amount. Support for the amendment to claim 6 can be found at least on page 4, lines 10-20. A copy of all of the pending claims as they are believed to have been amended is attached to this Amendment as an appendix.

The present invention is directed to the discovery that one can kill cells that have presented on their surfaces antigens derived from molecules that are characteristic of a virus, pathogenic bacterium, or infectious protein. As discussed in detail below, the antigens that are displayed on the surface by MHC I molecules are abnormal because they are over-expressed, derived from a source not normally present in the normal functioning cell (such as a bacterium, virus, or infectious protein), or mutated.

Rejection Under 35 U.S.C. § 112, first paragraph

Claims 1-8, 14-18, 25-26, and 28-29 were rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a

way as to reasonably convey to one skilled in the art that the inventor had possession of the claimed invention. Applicant respectfully traverses this rejection.

The applicant respectfully submits that the specification teaches and provides support for "killing cells in a patient", "kill the presenting cells", and "cells to be killed". For example, if the selected peptides are produced in the tumour cells, CTLs display tumour cell *killing* (see page 58, lines 11-12). The selected peptides, to which lines 11 and 12 refer, are "*presented* by HLA-A0201 class I molecules which are expressed by the antigen *presenting* cells" (see page 58, lines 7-8). Furthermore, Example 3, entitled "Adaptive Immunotherapy Using CTL *in Humans*" is supported by data presented in Figure 7 illustrating cell *lysis* by a CTL clone. In view of page 47, lines 9-13, wherein the level of *cell lysis* (lines 9-11) is translated into *killed* RMA lymphoma cells (lines 11-13), applicants respectfully submit, that the terms "lysis" and "kills" are viewed in the art as being synonymous and may be used interchangeably. "To lyse" is the equivalent of "to kill" in the presently claimed invention.

The Examiner states that there is no support for the phrase, "the cells to be killed". Page 51, lines 28-30, illustrates that the CTL can discriminate between transformed and normal cells, "killing specifically K^b positive melanoma and lymphoma tumours but not K^b expressing dendritic cells", therefore distinguishing between *cells to be killed* and cells *not* to be killed. Furthermore, page 42, line 2, states, "the CTL kill tumor cells *in vitro* whilst normal cells are not recognized".

It is also well known in the art that cytotoxic T-cells directly kill target cells. In one strategy, a lymphotoxin secreted by the CTL called perforin perforates the target cell membrane

causing transmembrane channels to form. This results in cell death via cell lysis. Alternatively, CTL may activate cell surface receptors, thereby inducing the cell to undergo programmed cell death (apoptosis).

In view of the foregoing discussion, applicant respectfully submits that the presently claimed invention is fully supported by the specification.

Claims 1-8, 14-18, 25-26, and 28-29 have been rejected under 35 U.S.C § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The Examiner states that specification fails to disclose any examples of either abnormal molecules or a mutant polypeptides. As provided in the foregoing discussion, the applicants submit that the specification is replete with examples of abnormal antigens and mutant polypeptides. The definition of "abnormal *antigen*" is derived from the specification. An abnormal antigen is defined, for example, on page 7, lines 24-28, in view of lines 3-22 on the same page. Abnormal antigens are any proteins expressed at high levels, proteins that are mutated in tumors, virally encoded proteins. CTL recognize these antigens that are displayed by MHC I molecules on the surfaces of cells. An abnormal antigen, by definition, is one that is not normal (i.e. not wild type, present in a diseased cell (mutated or foreign antigen) but not disease-free cell (self-antigen), over- or under-expressed). The examples provided on pages 17 and 18 define the characteristics of those antigens considered to be abnormal in the present specification. For example, "*normal* cellular proteins that are expressed at abnormally high

levels" or "*normal* cellular proteins that are mutated in tumours" are not normal. Once they are mutated or expressed at higher levels, they become abnormal. Furthermore, mutated proteins in tumors, virally encoded proteins in tumors, HIV encoded proteins in infected patients and bacterium encoded proteins in infected cells are inherently abnormal antigens compared to the non-diseased state of the cells (see lines 14-23, bridging pages 17 and 18). An abnormal antigen and the diseased state of a cell go "hand-in-hand". Without one you cannot have the other. As provided for in the specification, tumors typically induce the over-expression of what would *otherwise* be "normal" proteins. Examples include cyclin D1, cyclin E, mdm 2, EGF-R, erb-B2, etc. (page 7, lines 3-7).

Rejection Under 35 U.S.C. § 112, second paragraph

Claims 1-8, 14-18, 25-26, and 28-29 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

The Examiner states that the term "abnormal molecule" is indefinite because the term has not been defined in the specification. The definiteness of claim language must be analyzed, not in a vacuum, but in light of: (A) the content of the particular application disclosure; (B) the teachings of the prior art; and (C) the claim interpretation that would be given by one possessing the ordinary skill level in the pertinent art at the time the invention was made. MPEP 2173.02. The definition of "abnormal *antigen*" is derived from the specification. An abnormal antigen is defined, for example, on page 7, lines 24-28, in view of lines 3-22 on the same page. Abnormal antigens are any of proteins expressed at high levels, proteins that are mutated in tumors, virally

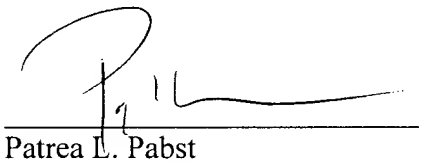
encoded proteins. CTL recognize these antigens that are displayed by MHC I molecules on the surfaces of cells. An abnormal antigen, by definition, is one that is not normal (i.e. not wild type, present in a diseased cell (mutated or foreign antigen) but not disease-free cell (self-antigen), over- or under-expressed). The examples provided on pages 17 and 18 define the characteristics of those antigens considered to be abnormal in the present specification. For example, "*normal* cellular proteins that are expressed at abnormally high levels" or "*normal* cellular proteins that are mutated in tumours" cannot be defined as normal. Once they are mutated or expressed at higher levels, they become abnormal. Furthermore, mutated proteins in tumors, virally encoded proteins in tumors, HIV encoded proteins in infected patients and bacterium encoded proteins in infected cells are inherently abnormal antigens compared to the non-diseased state of the cells (see lines 14-23, bridging pages 17 and 18). An abnormal antigen and the diseased state of a cell go "hand-in-hand". Without one you cannot have the other. As provided for in the specification, tumors typically induce the over-expression of what would *otherwise* be "normal" proteins. Examples include cyclin D1, cyclin E, mdm 2, EGF-R, erb-B2, etc. (page 7, lines 3-7).

The Examiner has stated that the term "mutant polypeptide" has not been defined in the specification. However, polypeptide is well known in the art as a chain of amino acids joined together by peptide bonds. The terms "polypeptide" and "protein" are used interchangeably in the art. The specification has again provided examples of such mutant polypeptides (see, for example, page 17, lines 19-26). The key to the present invention is that the CTL recognize peptides (fragments produced from polypeptides) presented by MHC molecules on the surface of cells. The displayed peptides, and polypeptides from which they are derived, are the hallmark or

signature of the tumor, bacteria, or virus causing the diseased state. Therefore, the peptide and polypeptide derived from, or produced as a result of a mechanism induced by, any of these sources are considered to be abnormal. "Normal cellular proteins that are mutated..." as stated on page 17, line 19, are no longer normal. They are abnormal.

Allowance of claims 1-18 and 25-29 is respectfully solicited.

Respectfully submitted,



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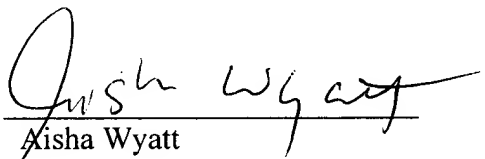

Aisha Wyatt

Date: September 27, 2001

Marked Up Version of Amended Claims

Pursuant to 37 C.F.R. § 1.121(c)(1)(ii)

1. (Three times amended) A method of killing cells in a patient with a disease characterized by expression by the patient of an abnormal [molecule] antigen or an abnormally elevated amount of a [molecule] antigen as compared to the non-diseased state, or by expression of an infectious agent protein, the method comprising

administering to the patient a therapeutically effective amount of cytotoxic T lymphocytes (CTL),

wherein the CTLs have a different HLA class I complex (or equivalent) than the cells to be killed, and

the CTLs specifically recognize a peptide portion of the abnormal [molecule] antigen or [molecule] antigen which is abnormally elevated in patients with the disease or the infectious agent protein, when the peptide is presented by the HLA class I complex (or equivalent) on the surface of cells to be killed, wherein the HLA class I complex (or equivalent) type presenting the peptide in the cells to be killed is not present in the CTLs to be administered to the patient, and

the CTLs kill the presenting cells.

2. A method according to Claim 1 wherein the CTL are a clonal population of CTL.

3. (Amended) A method according to Claim 1 wherein the CTL are substantially free of other cell types.

4. (Twice amended) A method according to Claim 1 wherein the [molecule] antigen is a polypeptide.